REMARKS

Status of Claims

Claims 1, 10-13, 15 and 23-43 are pending in the application.

Claims 1, 10-15 and 23-43 have been rejected.

By way fo this amendment, new claims 44-58 have been added.

Upon entry of this amendment, claims 1, 10-13, 15 and 23-58 will be pending.

Summary of the Amendment

New claims 44-58 correspond to claims 10 11, 12, 13, 15, 23-27,30-32, 35 and 36, respectively except each of claims 44-58 are dependent upon claim 40. Support for the amendment is found throughout the specification and claims as originally filed. No new matter has been added.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-10-13, 15 and 23-43 stand rejected under 35 U.S.C. §112, first paragraph, because , it is asserted, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. Applicant respectfully disagrees.

It is asserted in page 3 of the Official Action that

> …in the absence of working example; art recognized correlation between reducing the binding affinity of therapeutic antibody to FcRIIB and enhancing cytotoxicity elicited by said antibody, absent the ability to predict which of these antibodies would function as claimed, and given the lack of data on regions critical for said activity, one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.
>
> … …

> Since there is no working examples in the specification to show that by only reducing the binding affinity of therapeutic antibody to FcRIIB it is possible to enhance cytotoxicity of said antibody, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity as required to practice the invention.
>
> It is also noted, that the reference submitted by Dr. Ravetch in his CFR 1.132 Declaration further supported the Examiner position. In said reference, Shields et al., explicitly teach that "given the possible involvement of FcR in mechanism of action of therapeutic antibodies, human IgG1 variants with **improved binding capacity to human FcR, especially variants with better binding to Fc RIIIA** and simultaneously abrogation of binding to the inhibitory Fc RIIB could be used to provide more efficacious therapeutic antibody" (emphases added). In other words, even the reference provided by Applicant, teaches that therapeutic antibody should retain or improve its binding to activating Fc receptor, i.e., to FCRIIA and Fc RIII A.

The enablement rejection as set forth above appears based upon an asserted lack of enablement of claims which do not specifically require that the therapeutic antibody should retain or improve its binding to activating Fc receptor, i.e., to FCRIIA and Fc RIII A. Applicant notes that claims 39-43 (and new claims 44-58) include this limitation so this basis of the rejection does not apply to such claims. As applied to claims 1, 10-13, 15 and 23-38, Applicant respectfully urges that while Shields does suggest the desirability of therapeutics antibodies with reduced affinity to FcγRIIB while having retained or improved their binding to activating Fc receptor, i.e., to FCRIIA and Fc RIII A, Shields dos not state this as a requirement. That is, Shields does not state that variants with abrogated binding to the inhibitory Fc RIIB **must have** retained or improved binding capacity to human activating FcR. When all of the evidence is viewed in its entirety, one skilled in the art would accept Applicants assertion that the invention as claimed is enabled. The evidence of record supports this conclusion. While the evidence reflects the desirability of embodiments in claims 39-58, the evidence does not supports a finding that the subject matter in claims 1, 10-13, 15 and 23-38 is not enabled. Rather, when

viewed in its entirety, one skilled in the art would conclude that the specification enables one skilled in the art to practice the claimed invention.

The Official Action states in the paragraph bridging pages 3 and 4 and the paragraph thereafter that

> A description of a protein by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention. See Fiers, 984 F2d at 1169-71, 25 USPQ2D at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many species may achieve that result. The definition requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 /f.2d 1516, 1521, 22 USPQ 369, 372-73 (Fed. Cir. 1984) affirming the rejection because the specification does "little more than outline[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of (e.g., structural feature), is not a description of that material.
>
> Since the instant fact pattern fails to indicate that representative number of structurally related compounds, i.e., the genus of antibodies that have a reduced binding affinity for FcRIIB, due to modification of Fc portion of the antibody, that can be used in a method of enhancing cytotoxicity, the artisan would not know the identify of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

Applicant respectfully urges that the claims define **both** structure **and** function. Claim 1 expressly states that the "Fc region of the antibody is at least 80% homologous with a native Fc region." Claims 23-38 and 49-58 contain further structural limitations. Contrary tot the assertions in the Official Action, the structure of the antibodies are described as are the functional properties. The subject matter of the claims is described in and enabled by the

specification. One skilled in the art would recognize that applicant was in possession of the claimed invention and enabled its practice at the time the application was filed.

The Official action states on page 4 that:

> It is the examiner position that the specification does not provide sufficient guidance and examples as to which modifications would be acceptable to retain these specific structural and functional properties of claimed antibodies to be used in the claimed method for enhancing cytotoxicity elicited by antibody *in vivo*, which method comprises disrupting activation of SHIP by FcRIIB. In addition, the term "modifying" encompasses any substitution, deletion or insertion (page 14, lines 13-16 of the Specification as filed) of Fc portion of the antibody that will affect their structural and functional properties. Applicant acknowledges that single amino acid replacement in Fc portion of the mouse anti-HER2 antibody 4D5 reduces affinity for **both** FcRII and FcRIII receptors (page 35, lines 5-20 of the Specification as filed). The references cited by the examiner indicated that protein chemistry is probably one of the most unpredictable areas of biotechnology and that it is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function.

Applicant respectfully urges that it is well settled that the amount of routine experimentation may be large and still not be undue experimentation. One skilled in the art would have a reasonable expectation of success in practicing the claimed invention despite the need to perform routine experimentation. Thus, the experimentation is not undue. Similar to the facts in *In re Wands*, it may be necessary to produce and screen a large number of antibodies, in the instant case with modifications of the Fc region as variously structurally defined in each of the claims. Producing such antibodies would be routine as would be identifying which specific antibodies have the functional limitations set forth in the claims.

The totality of evidence on the record supports a conclusion that the claims are enabled. One skilled in the art could make and use the claimed invention without undue experimentation.

Applicant respectfully requests that the rejection of claims 1-10-13, 15 and 23-43 under 35 U.S.C. §112, first paragraph, as not being enabled by the specification be withdrawn.

Conclusion

Applicants submit that claims 1, 10-13, 15 and 23-58 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

As indicated on the transmittal accompanying this response, the Commissioner is hereby authorized to charge any debit or credit any overpayment to Deposit Account No. 50-0436.

Respectfully Submitted,

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